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STEREOSELECTIVE SYNTHESIS OF A NEW ALDOSE REDUCTASE INHIBITOR - AN EXTENSION OF THE BISLACTIM ETHER METHOD FOR THE SYNTHESIS OF AMINO ACIDS[1]

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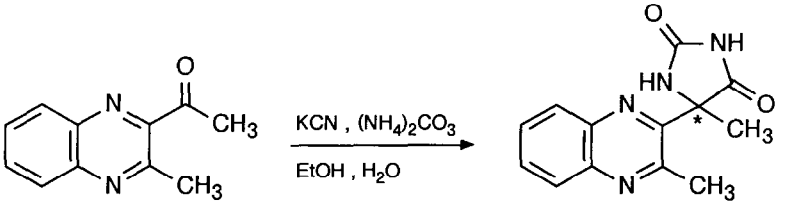
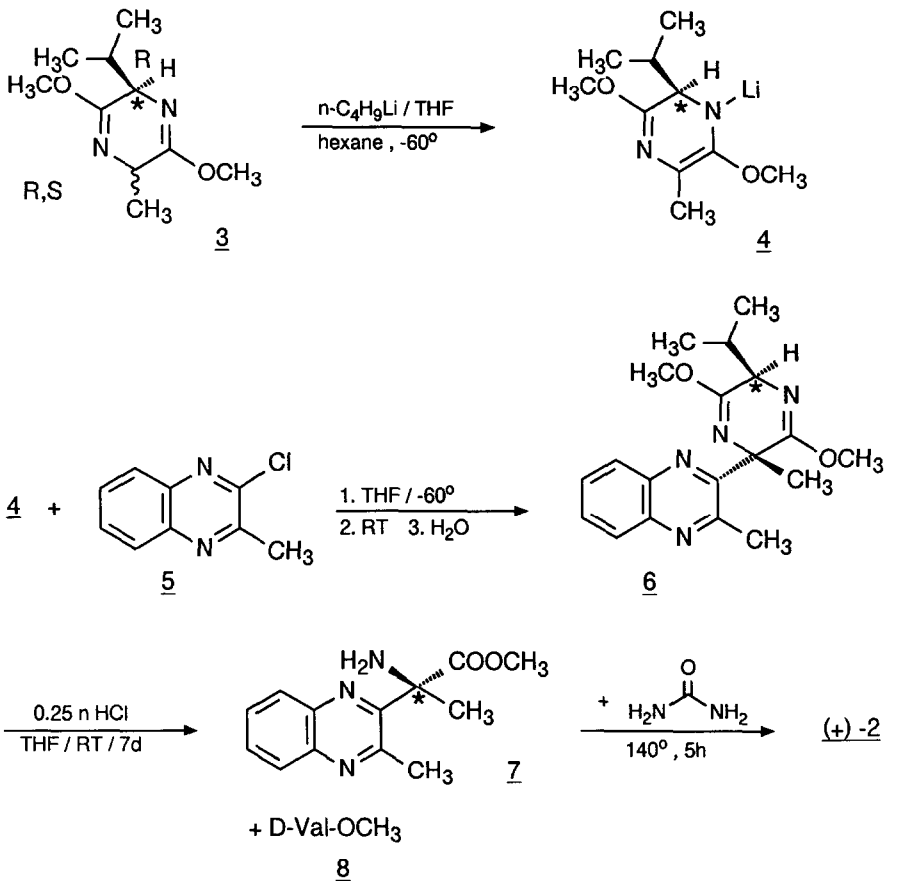
Summary: The stereoselective synthesis of the imidazolidinedione (+)-2, an inhibitor of aldose reductase, has been achieved via heterocyclic bislactim ether substitution, acidic cleavage and cyclization with urea.

Inhibitors of aldose reductase (EC 1.1.1.21) are expected to offer a therapeutical access to the late complications of diabetes mellitus.[2,3] The enantiomers of chiral aldose reductase inhibitors, e.g. Sorbinil®, show markedly different activities in vitro and in vivo.[3,4] This was also demonstrated for the enantiomers of the highly potent quinoxalinyl-imidazolidinedione 2.[5]



1 (±)-2

Both stereoisomers were first obtained by resolution of the racemic 2,[5] which was synthesized from 1[6] via a typical Bucherer-Bergs procedure using a twofold excess of potassium cyanide and five equivalents of ammonium carbonate in ethanol/water.[5,7] Repeated recrystallization of the corresponding brucine salt from ethanol and cleavage of the salt by column filtration (SiO_2, EtOAc/MeOH=1/1) led to about 3/1 mixtures of enantiomers[8] that were further purified by fractionating crystallization (MeOH/EtOAc=1/1, m.p. 203-204°C, $[\alpha]_D^{25}$= -52.4° and +52.5° resp., c=1 in EtOH, ee=98%, established by ^{1}H NMR plus shift reagent as described for (+)-2 in the experimental part). Unfortunately, the biologically more active (+)-2 had to be isolated from the mother liquor while the (-)-enantiomer directly crystallized with brucine.[5]



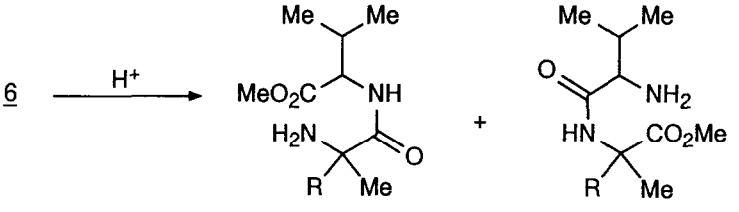
A stereoselective synthesis of the desired (+)-2 was achieved by modifying the bislactim ether method for the synthesis of (unnatural) amino acid esters.[9] Starting with the readily available 2R,5R,S-stereoisomer of the bislactim ether[10] 3 the intermediate 4 was generated by deprotonation with n-butyl lithium in THF. The reaction with 2-chloro-3-methylquinoxaline[11] (5) at -60°C and aqueous work-up gave the substitution product 6 in 69% yield and de≈95%, determined by the ^{1}H NMR spectrum.[10]

In analogy to simple alkyl substitution the stereoselectivity of this heteroarylation can be rationalized by the steric demand of the bulky quinoxaline residue that obviously is directed into the trans-position of the pyrazine ring by the isopropyl group.[10]

The cleavage of 6 with 0.25 N HCl requires a reaction time of five to seven days. The crude mixture of amino acid esters resulting upon usual work-up has to be separated chromatographically. As the bulky quinoxaline residue in 7 and the methyl group of 8 make the two cleavage products sufficiently different, the chromatographic separation in this case is

superior to the widely used Kugelrohrdestillation of structurally very similar products.

Spectra of byproducts obtained in very small amounts during chromatography indicate that also only one C=N double bond of the bislactim ether may be cleaved while the other one is stabilized by peptide bond formation (6 ⟶ 9 + 10).



9 10

R = 3-methyl-quinoxalin-2-yl

The behaviour of the quinoxalinyl substituted bislactim ether 6 towards acidic cleavage is surprisingly similar to alkyl derivatives and clearly different from acyl bearing analogues. E.g. a benzoyl-isopropyl-bislactim ether only gives benzoic acid and the constitutive esters Val-OCH_3 and Ala-OCH_3.[9,12]

Cyclization of the alanine ester 7 to the imidazolidinedione (+)-2 is achieved in a one-pot procedure. Heating 7 with 5 to 10 equivalents of urea followed by aqueous work-up and column filtration gives (+)-2 in 40% yield and ee=99% (detection limit).[13] Although the yield is only moderate, this cyclization covers several steps that otherwise would require some discrete reactions.

According to the usual (R ⟶ S) stereoselection[9,10] of bislactim ether substitution one may assume the 5-(S)-configuration of (+)-2 although this is not yet confirmed unambiguously. This also would correspond to the configuration and activity pattern of other enantiomerically pure aldose reductase inhibitors.[4]

The stereoselective formation of 6 seems to be the first example of a nucleophilic substitution of a heterocycle by bislactim ethers. This also means an extension of the scope of the bislactim ether method for amino acid synthesis. The short reaction sequence makes the desired biologically more active enantiomer easily available, especially in comparison with the time consuming resolution process and also with a stereoselective synthesis described for spiro imidazolidinediones.[14]

Acknowledgement - I thank my colleagues Dr.H.-W.Fehlhaber and Dr.V.Teetz for carrying out the NMR and HPLC work and helpful advice.

Experimental

Melting points were obtained with a Büchi apparatus (Dr.Tottoli) and are uncorrected. IR spectra were recorded on a Perkin Elmer 683 spectrometer. NMR spectra were recorded on Bruker WP 60, AM 270 or AM 400 spectrometers and mass spectra were run on a Kratos MS 80 RFA instrument. Optical rotations were measured using a Perkin Elmer polarimeter type 141. Elemental analyses were carried out by the Zentrale Analytik, Hoechst AG, Frankfurt.

5-Methyl-5-(3'-methyl-quinoxalin-2'-yl)-imidazolidine-2,4-dione ((±)-2).- 25 g (0.134 mol) of 2-acetyl-3-methyl-quinoxaline,[6] 17.5 g (0.268 mol) of KCN and 64.4 g (0.67 mol) of $(NH_4)_2CO_3$ are dissolved in 445 ml of ethanol/water (1/1) and the solution is stirred at 60°C for 72 h. Then the mixture is carefully acidified with half-concentrated HCl, while cooling and neutralizing the evolved HCN and the precipitate formed is filtered off with suction. The residue is washed with water and taken up in 1 N NaOH, and the mixture is extracted with ether. The aqueous layer is acidified with half-concentrated HCl under cooling, and after filtration and washing the product is recrystallized from ethanol or MeOH/EtOAc = 1/1 to give 24.4 g (74%) of (±)-2, m.p. 225-227°C; ν_{max} (KBr) 3310, 3220, 3060-3010, 2760-2720, 1770, 1730-1705, 1390, 760 cm^{-1}; δ_H (60 MHz; D_6-DMSO) 1.95 (3H, s), 2.63 (3H, s), 7.65-8.25 (4H, m), 8.53 (1H, br. s, D_2O exch.), 11.33 (1H, br. s, D_2O exch.); m/z 257 (M^++H), 213 (M^+-CH_3 -CO), 143; found: C, 60.85; H, 4.7; N, 21.75 %; requires: C, 60.93; H, 4.72; N, 21.86%.

(5'R)-2-(5'-Isopropyl-3',6'-dimethoxy-2'-methyl-2',5'-dihydropyrazine)-3-methyl-quinoxaline (6) - 25 g (0.126 mol) of (2R),(5R,S)-2-isopropyl-3,6-dimethoxy-5-methyl-2,5-dihydropyrazine[10] in 330 ml of dry THF are cooled under argon to -60°C and 84 ml of a 15% solution of n-butyl lithium in hexane are added dropwise. After 30 min at -60°C a solution of 22.5 g of 2-chloro-3-methyl-quinoxaline[11] in 330 ml dry THF is added and the reaction is monitored by TLC. After completion (~1.5 h), 6 ml water are added dropwise and the mixture is allowed to reach ambient temperature. The solvents are evaporated, the residue is diluted with ether, and the solution is washed with water. The product obtained after drying and removal of the solvent under reduced pressure is further purified by recrystallization from CH_3CN or hexane with charcoal to give 29.6 g (69%) of 6, m.p. 113-114°C; ν_{max} (KBr) 2965, 2940, 2870, 1685, 1435, 1285, 1245, 755 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 0.8-1.3 (6H, dd), 1.95 (3H, s), 2.4 (1H, m), 2.5 (3H, s) 3.6 (6H, s), 4.2 (1H, d, J 4 Hz), 7.6-8.25 (4H, m); m/z 341.2 (M^++H), 325

(M^+-CH_3), 309, 240, 197, 155; found: C, 67.0; H, 7.0; N, 16.3%; requires: C, 67.04; H, 7.11; N, 16.46%.

(+)-2-(Quinoxalin-2'-yl)-alanine methyl-ester (7).- 11.9 g (0.035 mol) of the quinoxaline 6 are suspended in 870 ml 0.25 N HCl and 870 ml THF are added. The mixture is stirred at room temperature for seven days. The THF is removed under reduced pressure and the aqueous phase is extracted several times with ether. After addition of aqueous ammonia (pH 8-10) the product is extracted with ether and further purified chromatographically using SiO_2 and EtOAc/hexane = 2/1 for elution. One obtains 5.86 g (68%) of 7 as a sligthly yellow oil that crystallizes upon standing. The product is recrystallized from Et_2O/hexane using a refrigerator; m.p. 73°C; ν_{max} (KBr) 3375, 2950 1745, 1570, 1440, 1215, 765 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.9 (3H, s), 2.3 (2H, br. s, D_2O exch.), 2.75 (3H, s), 3.8 (3H, s), 7.6-8.2 (4H, m); m/z 245.9 (M^++H), 185.9, 143.9, 101.9; found: C, 63.50; H, 6.15; N, 17.15; O, 12.80%; requires: C, 63.66; H, 6.16; N, 17.13; O, 13.05%; $[\alpha]_D^{25}$ +45.5° (c=1, EtOH).

(+)-5-Methyl-5-(3'-methyl-quinoxalin-2'-yl)-imidazolidine-2,4-dione ((+)-2). 3 g (12.2 mmol) of the alanine ester 7 are added to 4.5 g (75 mmol) of urea and the mixture is heated to 130°-140°C for 4 h. After cooling the mixture is treated with EtOAc and water, the organic layer is separated, dried over $MgSO_4$, and the solvent is evaporated. The residue is purified by column chromatography (SiO_2, EtOAc/hexane = 2/1). Recrystallization from EtOAc/MeOH gives 1.25 g (40%) of (+)-2, m.p. 203°-204°C; ^1H NMR (60 MHz), IR and mass spectra of (+)-2 are identical to the corresponding spectra of the racemate (±)-2. δ_H (400 MHz, $CDCl_3/CD_3OD$) 2.1 (3H, s), 2.8 (3H,s), 7.7-7.8 (2H, m), 8.0-8.1 (4H, m); no peak separation of the CH_3-singuletts upon portionwise addition of shift reagent (S)-(-)-1-(anthracen-9'-yl)-2,2,2-trifluoroethanol (detection limit: ee = 99%; analogous analysis of (+)-2 obtained by resolution with brucine gives peak splitting with ee = 98%); found: C, 60.5; H, 4.8; N, 21.7%; requires: C, 60.93; H, 4.72; N, 21.86%; $[\alpha]_D^{25}$ +53° (c=1, EtOH).

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